J. Braz. Chem. Soc., Vol. 20, No. 1, 42-45, 2009.
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0103 - 5053 $6.00+0.00

Article

SiO_2·*p*-TSA: a Green Catalyst for Solvent-free Tetrahydropyranylation of Alcohols and Thiols

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Foi desenvolvido um procedimento para tetrahidropiranilação de álcoois e tióis em ausência de solvente orgânico, baseado na simples mistura dos reagentes, na presença de sílica gel e quantidade catalítica de *p*-TSA.

A solvent-free procedure for tetrahydropyranylation of alcohols and thiols based on a simple grinding of the reagents in the presence of silica gel and catalytic amounts of *p*-TSA is described.

Keywords: solvent-free, tetrahydropyranyl ether, catalyst, alcohols, thiols

Introduction

The protection of functional groups must be avoided whenever it is possible. However, when it is not possible, practical and friendly conditions must be employed to perform the protection reaction.

Alcohols are among the functions most frequently protected and deprotected in a synthetic sequence. Tetrahydropyranyl is one of the most popular protecting groups for this purpose. The common protocol for the tetrahydropyranylation of alcohols consists in their reaction with dihydropyran in dichloromethane in the presence of an acid catalyst.[1] Many alternative methodologies and reagents were developed for protection of alcohols, including protic and Lewis acid catalysts such as montmorillonite K-10, Amberlyst®, zeolites, $ZnCl_2$, I_2, $La(NO_3)_3$, $BF_3{\cdot}Et_2O$, $Zr(O_3PCH_3)1{\cdot}2(O_3C_6H_4SO_3H)0{\cdot}8$, *p*-TSA (in solution),[1] $In(OTf)_3$, $NbCl_5$, $InCl_3$, H_2SO_4 on silica gel, $VO(acac)_2$, $Ru(acac)_3$, $PdCl_2(CH_3CN)_2$, $CeCl_3{\cdot}7H_2O$/NaI, AcCl and some others.[2] However, several of these methods present some drawbacks such as long reaction times, use of expensive, hazardous or toxic reagents or solvents, high temperatures, need of high catalyst to substrate ratios, moisture or water sensitive reaction conditions.

In this work we report a solvent-free acid catalyzed tetrahydropyranylation of alcohols and thiols based on a simple grinding of the reagents in the presence of silica gel and catalytic amounts of *p*-TSA.

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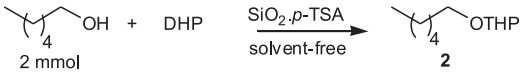
Results and Discussion

The best reaction conditions were determined by using *n*-hexanol as a model compound. In a preliminary experiment the reaction was performed by mixing silica gel (1 g) and *p*-TSA (2 mmol) in a mortar followed by addition of *n*-hexanol (2 mmol) and DHP (2.3 mmol). A very exothermic reaction takes place with partial carbonization of the organic materials, evidenced by the instantaneous formation of a black colour. We assume that is due to the high reactivity of DHP with *p*-TSA. To circumvent this problem the *n*-hexanol (2 mmol) and DHP (2.3 mmol) were homogenized with silica gel (0.5 g) in a mortar and in an other mortar silica gel (0.5 g) and *p*-TSA (2 mmol) were mixed and ground. Then the contend of the first mortar was added to the second one and the resulting clear solid mixture was ground for about 5 min. After this time, GC analysis showed the total consumption of the alcohol and the formation of the tetrahydropyranyl ether **2** in 50% isolated yield. In order to improve the yield, the reaction conditions were varied as shown in Table 1.

As can be observed in Table 1, the reaction works well even using sub-stoichiometric amount of *p*-TSA (0.08 equiv., Table 1, entry 4). However, when 0.025 equiv. of *p*-TSA was used (Table 1, entry 5) longer reaction time was necessary to consume *n*-hexanol, and compound **1**

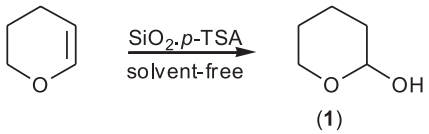
Table 1. Tetrahydropyranylation of 1-hexanol promoted by SiO_2/*p*-TSA catalyst in under solvent-free conditions



Entry	DHP / mmol	*p*-TSA / mmol	time / min[a]	Y / (%)[b]
1	2.5	2	5	50[c]
2	2.5	1	5	75
3	2.5	0.5	5	77
4	2.5	0.08	5	79
5	4.0[d]	0.025	>30	40
6	2.5	0	>60	0
7[e]	10	0.32	5	73

Reaction were conduced by mixing in a mortar SiO_2 (1 g), n-hexanol and the reagents; [a]grinding time in a mortar; [b]isolated yield; [c]compound **1** was isolated as by-product in 30% yield; [d]DHP was added in two portions: 2.5 mmol followed by 1.5 mmol after 20 min grinding; [e]the reaction was carried out with 10 mmol of the alcohol and 10 mmol of the DHP.

was detected as major product.[3] In the absence of *p*-TSA no reaction was observed even after 1 hour of grinding. In a separate experiment DHP (2 mmol) was ground in the presence of *p*-TSA (0.025 mmol) in silica gel (1 g) in absence of the alcohol. Product **1** was isolated in almost quantitative yield, after a few minutes grinding (Scheme 1). This product presumably is formed by the nucleophilic addition of the water present on the silica gel or from the monohydrated *p*-TSA to the protonated dihydropyran oxonium intermediate.



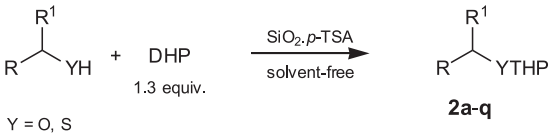
Scheme 1. By-product of reaction of DHP with SiO_2/*p*-TSA.

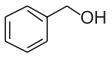
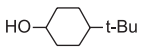
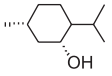
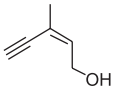
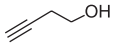
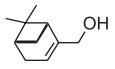
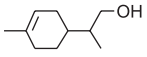
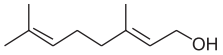
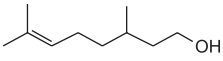
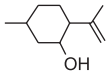
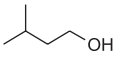
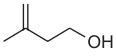
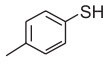
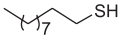
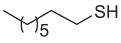
The *n*-hexanol was also reacted with DHP in a 10 mmol scale, yielding the corresponding THP ether (**2**) in similar good yield (Table 1, entry 7).

With these results in hand we submitted other alcohols to the reaction with DHP under the optimized experimental conditions[4] (Table 1, entry 4). Table 2 summarises the results of the protection reaction with saturated, unsaturated, primary, secondary, allylic and benzylic alcohols.

Benzyl alcohol required 10 min grinding to be consumed (Table 2, entry 1). The other alcohols were converted to the tetrahydropyranyl ethers within only 5 min. Tertiary alcohols and phenols failed to react under the reaction conditions of Table 2. We attribute these results to the lower reactivity of phenols[5] and to the steric hindrance of the tertiary alcohols.[6] On the other hand, thiols showed similar

Table 2. Tetrahydropyranylation of alcohols and thiols promoted by SiO_2/*p*-TSA catalyst under solvent-free conditions



Entry	Substrate	Product	time / min	Yield / (%)[a]
1		**2a**	10	90
2		**2b**[7]	5	75
3		**2c**[8]	5	80
4		**2d**[9]	5	83
5		**2e**[9]	5	88
6		**2f**[10]	5	77
7		**2g**[2,11]	5	70
8		**2h**	5	90
9		**2i**[2]	5	97
10		**2j**[11]	5	65
11		**2k**[12]	5	98
12		**2l**	5	81
13		**2m**[13]	5	80
14		**2n**[14]	5	79
15[b]		**2o**[15]	25	68[c] (8)[d]
16[b]		**2p**[2]	20	85[c] (10)[d]
17[b]		**2q**[16]	20	81[c] (8)[d]

[a]Isolated yield; [b]reactions were carried out on 1.0 mmol scale of thiol and 1.15 mmol of DHP in the presence of 80 mg of a mixture of *p*-TSA·SiO_2 (37.5% of *p*-TSA in SiO_2); [c]yields refer to the isolated Markovnikov product; [d]yields refer to the isolated anti-Markovnikov product.

good reactivity by this protocol yielding the corresponding thioethers. A solvent-free non catalyzed procedure for tetrahydropyranylation of thiols was described recently.[7] The authors were able to produce preferentially the anti-Markovnikov products by simply mixing under heating the both reagents (thiol and DHP). The reason of that preference is the existence of an interaction between the oxygen atom of the vinyl ether and the hydrogen of the thiol that activates the C-C double bond of the vinyl ether.[7] As expected for the acid catalyzed tetrahydropyranylation mechanism, by using our procedure those products were only observed as by-products (Table 1, entries 15-17). The isolation of the products was performed by transferring the resulting solid (for the alcohols) or the liquid mixture (for the thiols) to a chromatographic column and eluting with the appropriate solvent solution. In some cases the isolation consisted in a simple filtration through a pad of silica gel.

Conclusions

In summary, we have reported a simple, fast and cheap solvent-free method for the tetrahydropyranylation of alcohols and thiols. The protocol is eco-friendly since no solvent is needed to conduct the reaction and most of the products were purified by a simple filtration in silica gel with a reduced quantity of hexane and ethyl acetate. The method presented good generality and has been used in our laboratory in preparative scale.

Acknowledgments

The authors thank FAPESP, CNPq and CAPES for support.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.org.br, as PDF file.

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4. General procedure for the tetrahydropyranylation of alcohols on solvent-free conditions. Silica gel (0.5 g) and *p*-TSA (0.015g, 0.08 mmol) were homogenized in a mortar. In a separated mortar were ground, silica gel (0.5 g), benzyl alcohol (0.20 mL, 0.21 g, 2 mmol) and dyhydropyran (0.24 mL, 0.22 g, 2.6 mmol), then the first solid mixture was added to the second mortar and this resulting clear solid was ground for the specified time presented in Table 2. The product was isolated by transferring the solid mixture to the top of a chromatographic column followed by elution with a mixture of hexane:ethyl acetate (7.5:0.5), yielding 0.34 g (90%) of *2-(benzyloxy)-tetrahydro-2H-pyran* ***2a***: CAS 1927-62-4; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4-7.2 (m, 5H); 4.8 (d, *J* 12 Hz, 1H); 4.7 (t, *J* 3.2 Hz, 1H); 4.5 (d, *J* 12 Hz, 1 H); 4.0-3.9 (m, 1 H); 3.6-3.5 (m, 1 H); 1.9-0.8 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.2; 128.2; 127.6; 127.3; 105.1; 97.5; 68.6; 61.9; 30.4; 25.3; 19.2; *2-(2-methylcyclohexyloxy)-tetrahydro-2H-pyran* ***2b***:[8] CAS 218623-12-2; *2-(4-tert-butylcyclohexyloxy)-tetrahydro-2H-pyran* ***2c***:[9] CAS 80356-16-7; *2-((1 R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)-tetrahydro-2H-pyran* ***2d***:[10] CAS 128946-28-1; *tetrahydro-2-(pentan-2-yloxy)-2H-pyran* ***2e***:[10] CAS 122685-20-5; *2-((Z)-3-methylpent-2-en-4-ynyloxy)-tetrahydro-2H-pyran* ***2f***:[11] CAS 41967-81-1; *2-(but-3-ynyloxy)-tetrahydro-2H-pyran* ***2g***:[2,12] CAS 40365-61-5; *2-(((1R,5S)-6,6dimethylbicyclo[3.1.1]hept-2-en-yl)methoxy)-tetrahydro-2H-pyran* ***2h***: ^{1}H NMR (200 MHz, $CDCl_3$): δ (mixture of diastereoisomers) 5.50-5.49 (m, 1H); 4.64-4.59 (q, *J* 3.2 Hz, 1H); 4.09-4.00 (m, 1H); 3.92-3.82 (m, 2H); 3.54-3.44 (m, 2H); 2.43-2.27 (m, 2H); 2.19-2.09 (m, 2H); 1.90-1.78 (m, 1H); 1.65-1.49 (m, 4H); 1.29 (s, 3H); 1.22-1.16 (dd, *J* 3.6Hz and 5Hz, 2H); 0.84 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$): δ (mixture of diastereoisomers) 145.0; 144.9; 119.3; 118.8; 97.3; 97.0; 69.3; 61.8; 43.9; 43.2; 40.8; 37.9; 37.8; 31.3; 31.2; 31.1; 30.4; 26.0; 25.4; 20.9; 20.8; 19.3. IR (neat) ν_{max}/cm^{-1}: 2980, 2939, 2873, 1683, 1652, 1462, 1437, 1382, 1358, 1262, 1182, 1135, 1077,

1023, 979, 904, 869, 815, 800, 514. HRMS Calc. for $C_{15}H_{24}O_2$: 236.1776; found: 236.2669; *2-(2-(m-methylcyclohex-3-enyl) propoxy-tetrahydro-2H-pyran* ***2i***:[2] CAS 217438-56-7; *2-((E)-3,7-dimethylocta-2,6-dienyloxy)-tetrahydro-2H-pyran* ***2j***:[12] CAS 59632-99-4; *2-(3,7-dimethyloct-6-enyloxy)-tetrahydro-2H-pyran* ***2k***:[13] CAS 90243-41-7; *2-(5-methyl-2-(prop-1-en-2-yl)cyclohexyloxy)-tetrahydro-2H-pyran* ***2l***: ^{1}H NMR (200 MHz, $CDCl_3$): δ (mixture of diastereoisomers) 4.82-4.49 (m, 3H); 4.03-3.80 (m, 1H); 3.63-3.38 (m, 2H); 2.13-1.22 (m, 15H) 1.17-0.75 (m, 5H). ^{13}C NMR (50MHz, $CDCl_3$): δ (mixture of diastereoisomers) 148.1; 147.6; 111.1; 110.9; 110.3; 100.3; 93.5; 93.2; 79.1; 74.7; 62.6; 61.3; 52.1; 51.3; 43.2; 39.8; 34.9; 34.4; 34.2; 31.7; 31.3; 31.1; 30.9; 30.8; 30.6; 25.6; 25.5; 22.2; 22.1; 20.6; 20.1; 19.9; 18.9; 18.7. IR (neat) ν_{max}/ cm^{-1}: 3076, 2931, 2867, 2851, 1646, 1455, 1261, 1200, 1128, 1023, 975, 870, 816, 472. HRMS Calc. for $C_{15}H_{26}O_2$: 238.1932; found: 238.2828; *tetrahydro-2-(isopentyloxy)-2H-pyran* ***2m***:[14] CAS 60564-80-9; *2-(3-methylbut-3-enyloxy)-tetrahydro-2H-pyran* ***2n***:[15] CAS 55975-11-6; *2-(p-tolylthio)-tetrahydro-2H-pyran* ***2o***:[16] CAS 50686-30-1; *2-(decylthio)-tetrahydro-2H-pyran* ***2p***:[2] CAS 388090-91-3; *2-(heptylthio)-tetrahydro-2H-pyran* ***2q***:[17] CAS 98194-93-5;

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Received: June 19, 2008
Web Release Date: October 24, 2008

FAPESP helped in meeting the publication costs of this article.